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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,644	02/21/2002	Hiroaki Yamamoto	14879-100001/ D1-A0103-US	1965

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,644	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-58* is/are pending in the application.

4a) Of the above claim(s) *31-42* is/are withdrawn from consideration.

5)☒ Claim(s) *54 and 55* is/are allowed.

6)☒ Claim(s) *43-52 and 56-58* is/are rejected.

7)☒ Claim(s) *53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 31-58 are pending in the present application. In the prior action, mailed on August 13, 2003, claims 1-3, 16 and 17 were rejected, and claims 4-15, 18-42 were withdrawn as to nonelected inventions. In the Response, filed on December 9, 2003, the Applicant cancelled claims 1-30, and added new claims 43-58, which read on polypeptides encompassed by the previously rejected claims.

Claims 43-58 are pending and under consideration in the present application.

Specification

2. **(New Objection)** The disclosure is objected to because of the following informalities:

On page 11, the disclosure refers to a isolated polypeptide that "includes a nucleotide sequence that is ...identical to SEQ ID NO: 1." It appears that the term "polypeptide" in line 21 of page 11 should read polynucleotide.

On page 12, the disclosure refers to polynucleotides that "have the amino acid sequence of SEQ ID NO: 2..." It appears that the phase "polynucleotides that have" in line 14 of page 12 should read - - polynucleotides that encode.- -

Appropriate correction is required.

Claim Objections

3. **(New Objection)** Claim 47 is objected to because of the following informalities: the claim refers to the stringency conditions described in the claim as "stringent conditions." However, the application identifies less stringent conditions as "stringent conditions, and the indicated conditions as "high stringency." It is therefore requested that the claim be amended such that the claim language reads "high stringency" so as to be consistent with the terminology used in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. **(Prior Rejection- Withdrawn)** Claims 16 and 17 were rejected in the prior action under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. In view of the cancellation of these claims, and the inclusion of functional language in the newly added claims, the rejection is withdrawn.

Claim Rejections - 35 USC § 112

5. **(Prior Rejection- Withdrawn)** Claim 3 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim read on an enone reductase that "is derived from an organism or the genus Kluyveromyces." It was unclear what is meant by the phrase "derived from." In view of the cancellation of this claim, and the clarification in new claims 52 and 53 that the polypeptide is from a Kluyveromyces fungus, the rejection is withdrawn.

6. **(Prior Rejections- Withdrawn)** Claim 16 was rejected in the prior action under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment of the claims and the arguments pursuant thereto, the indefiniteness rejections made with reference to claim 16 in the prior action are withdrawn.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. **(New Rejection-Necessitated by Amendment)** Claims 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection. These claims, newly added to the application, read on polypeptides with enone reductase activity that are at least 85 or at least 95 percent identical to the sequence of SEQ ID NO: 2. The Applicant points to page 16, lines 3-7 as providing support for these claims. However, the disclosure on these pages sets the ranges of identity with SEQ ID NO: 2 at the ranges of at least 60, 70, 80, or 90 percent identical to the sequences of SEQ ID NOs: 4, 6, or 8. It is noted that page 13, lines 12-15 does provide support for these ranges of identity with SEQ ID NO: 2, but does not include ranges of at least 85% or 95% identity. Thus, the Application does not provide

written description support for the genus of inventions comprising polypeptides that are at least either 85 or 95 percent identical to SEQ ID NO: 2.

9. **(Prior Rejection- Withdrawn)** Claim 16 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the claim read, in part, on proteins encoded by "a nucleic acid that hybridizes under stringent conditions with a nucleic acid consisting of the nucleotide sequence of SEQ ID NO: 1, and that encodes a protein functionally equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2." In view of the cancellation of this claim, and because new claim 47 reads on polypeptides encoded by the complement of the hybridization partner of SEQ ID NO: 1, the rejection is withdrawn.

10. **(Prior Rejection- Maintained)** Claims 3 and 16 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for proteins of SEQ ID NO: 2, does not reasonably provide enablement for variants or fragments of this protein which are functional equivalents of SEQ ID NO: 2. These two claims have been cancelled, and replaced by claims 43-50, and 56-58, all of which read on enone reductase enzymes with an amino acid sequence that is a variant of SEQ ID NO: 2. The rejection is therefore withdrawn as moot with reference to claims 3 and 16, but is extended to new claims 43-50, and 56-58.

The Applicant traverses the rejection on the grounds that they have provided assays by which those in the art could determine if a particular variant has the required enone reductase activity, and because making variants of SEQ ID NO: 2 is within the easy capability of those in the art. The Applicant argues "[a]ll methodologies for performing [the processes of alteration and

the assays to determine activity] are routine and well known in the art and/or disclosed in the present specification and require no inventive effort or thought." Response page 11. These arguments are not found persuasive.

In the prior action, it was argued that the art of protein modification is complex and wrought with unpredictability. As indicated in the Bowie reference cited in the prior action, the art teaches that when making alterations to a protein sequence, the effects of a particular mutation are generally unpredictable even though proteins are generally able to accommodate some mutations within its sequence. While the reference indicates that a conservative substitution may be more acceptable that otherwise, the reference also indicates that even conservative substitutions may not be tolerated by the protein (i.e., may cause loss of function). The reference indicates that this unpredictability stems from the lack of information regarding the relationship between the mutated residues, and the structure or function of the protein as a whole. See, page 1306. Further, the art also indicates that, except in certain circumstances, the effects of multiple changes to a proteins sequence are additive. See, Wells, Biochemistry, 29: 8509-8517. From these teachings it is, however, also indicated that knowledge of the active region of the protein, thus knowing what residues had to be maintained, or the effects that modification of those residues would have, reduces the unpredictability involved.

As indicated in the prior action, the Applicant has provided little guidance as to what residues in SEQ ID NO: 2 are required for the indicated enone reductase activity. While the Applicant has provided three examples of proteins with enone reductase activity from other proteins, the homologous regions among these proteins are several and disperse, thus providing few clues as to which regions are actually responsible for the indicated activity. Thus, there is

limited guidance, to counter the known complexity and unpredictability of protein modification, as to what residues may be modified by those in the art without loss of activity. Further, while the newly added claims are more limited in scope than the previously rejected claims in that they limit the number of modifications that may be made, they still cover a large genus of enone reductases. Aside from SEQ ID NO: 2 itself however, the application does not disclose any other enone reductases that fall within the bounds of the current claims. Thus, to support the broad claims to variants of SEQ ID NO: 2 with enone reductase activity, the Applicant has provided little guidance and no working examples of variants meeting the claim limitations, that those in the art could use to counter the unpredictability inherent in protein modification in the practice of the claimed invention. For these reasons, and for the reasons of record, the rejection is maintained against newly added claims 43-50, and 56-58.

Applicant's arguments with respect to claims 51-53 on page 11 of the Response are noted. These arguments will be considered below in rejections specific to these claims.

11. **(Prior Rejection- Maintained)** Claims 1-3 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. While claims 1-3 have been cancelled, the Applicant has added new claims 51-53. These claims read on any enone reductase that meets certain physical property limitations. Claims 52 and 53 further limit the claimed enzymes to those from either any Kluyveromyces fungus, or any enone reductase of Kluyveromyces lactis, with the claimed characteristics. The Applicant has identified the claimed genus through identification of chemical properties of a disclosed protein. However, the Applicant has provided only one example of a protein with the desired characteristics- the

protein of SEQ ID NO: 2. See, App., pages 29-31. As indicated in the prior action, while three other proteins are disclosed as enone reductases, these proteins have not been shown to have the other chemical properties required by the claims. It is further noted that these other proteins are not from Kluyveromyces cells. Nonetheless, the claims are written such that they may cover more than just SEQ ID NO: 2.

The rejection is therefore extended to new claims 51 and 52 because the Applicant has not established that any enone reductase, or any enone reductase isolated from any Kluyveromyces, would meet the claim limitations. The requirements for satisfying the written description requirement with reference to a genus of inventions was provided in the prior action. In the present case, because the Applicant provides only one example of an enone reductase that meets the claimed limitations, the Applicant has not provided sufficient written description support for the claimed genus. While other enone reductases may meet the claim limitations, the Applicant has not demonstrated that they are in possession of such other enzymes. There is no indication that enone reeducates of other Kluyveromyces have the required characteristics, or that any enone reductase with the indicate molecular weight would meet the other limitations of the claims. For these reasons, and for the reasons of record, the rejection is maintained over new claims 51 and 52.

The rejection is not extended to claim 53 because the Applicant has demonstrated that an identified enone reductase from Kluyveromyces lactis meets the claimed limitations.

12. **(Prior Rejection- Maintained)** Claims 1-3 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the enone reductase of SEQ ID

NO: 2, does not reasonably provide enablement for other enone reductases that have the chemical properties according to the identified claims. As noted above, while claims 1-3 have been cancelled, the Applicant has added new claims 51-53. Therefore, although the rejection is withdrawn as to claims 1-3 as moot, the rejection is extended to, and maintained over, claims 51 and 52.

These claims were described above. The Applicant is not enabled for the full extent of the claimed invention because the Applicant has not enabled those in the art to make or acquire any enone reductase with the claimed properties. The Applicant has neither established that any other enone reductase isolated from any Kluyveromyces cell would meet all of the claimed limitations, or indicated from what organisms proteins with these properties may be isolated. While the Applicant has provided three examples of enone reductase proteins from other cells, the Applicant has not established that these proteins share all of the properties possessed by SEQ ID NO: 2, and identified in the claims. In view of the fact that the claims read broadly on any enone reductase with the claimed properties, the that Applicant has disclosed only one example of a protein with these properties, and that the Applicant has provided little guidance as to how to make other proteins that have each of the claimed properties, the Applicant is not enabled for the full scope of the rejected claims.

13. **(Prior Rejection- Maintained)** Claims 3, 16, and 17 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. As indicated above, these claims have been cancelled from the application, and

replaced by claims 43-50, and 56-58. The rejection of these claims is maintained for the reasons of record.

The Applicant argues that the newly added claims "simply do not allow for a substantial amount of variability in structure or functions of the claimed polypeptides." However, while the Examiner agrees that the current claims are less extensive than the previously rejected claims, the Examiner is not convinced that the Applicant has provided sufficient written description support for the presently claimed genus. In particular, while the Applicant has provided four examples of enone reductases (only SEQ ID NO: 2 of which falls within the scope of the present claims), there is insufficient information provided by the Applicant to support claims to any variant of SEQ ID NO: 2 that falls within the indicated claims. Because the Applicant has neither provided any examples of variants of SEQ ID NO: 2 that maintain the enone reductase activity, or provided any guidance linking the enzymatic function to a known or disclosed structure, the Applicant has not provided sufficient information to support the claimed genus. While the Applicant has provided other examples of proteins with enone reductase activity with some homology to SEQ ID NO: 2, neither the Applicant nor the art has identified from these examples a common structure that is associated with the required activity. Thus, the application has not provided sufficient information to demonstrate the Applicant is in possession of the full scope of the claimed genus.

The Applicant further argues that according to the rationale of Example 14 of the January 5, 2001 guidelines, the current claims have adequate written description support. However, it is noted that in that Example, both the catalytic activity of the claimed proteins, and a sequence of SEQ ID NO: 3 are essential to operation of the claimed genus. Thus, read in view of the Eli Lilly

decision cited in the prior action, in that example there has been a disclosure of an activity associated with a specific sequence. In the present case, while the Applicant has provided a sequence, there has been no identification of a particular sequence that is associated with the claimed function. Thus, absent such a correlation of function and structure, the Applicant has not provided adequate written description support for the rejected claims.

Furthermore, as indicated in the enablement rejection of these claims above, in view of the lack of a disclosed association between the claimed function and any identifiable structure, it is apparent that there is a high level of unpredictability regarding what variants of SEQ ID NO: 2 would maintain their enone reductase activity. The Federal Circuit recently held that an inventor of "a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." Noelle v. Lederman (Fed Cir, No. 02-1187, 1/20/04). In the present case, there is unpredictability regarding the properties of sequences other than SEQ ID NO: 2. For these reasons, and the reasons of record, the rejection is maintained over new claims 43-46, 48-50, and 56-58.

Claim Rejections - 35 USC § 102

14. **(Prior Rejection- Withdrawn)** Claim 16 was rejected under 35 U.S.C. 102(b) as being anticipated by Shimoda et al., Phytochemistry 49(1): 49-53, Wanner and Tressl, Eur. J. Biochem 255:271-78, and Kawai et al., Tetrahedron Letters 39:5225-28 (all of record in the IDS filed on July 30, 2002). As indicated above, claim 16 reads on the polypeptides encoded by the nucleic

acids of claim 6. In view of the cancellation of claim 16, and the limitations regarding sequence identity in the newly added claims, the rejection is withdrawn.

Conclusion

15. Claims 54, and 55 appear to be allowable over the prior art. The protein of SEQ ID NO: 2 appears to be free of the art.

16. Claim 53 is objected to as depending from a rejected claim.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 2/23/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600